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The immunology and genetics of resistance of sheep to *Teladorsagia circumcincta*

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## Abstract

*Teladorsagia circumcincta* is one of the most economically important gastrointestinal nematode parasites of sheep in cool temperate regions, to which sheep show genetically-varying resistance to infection. This is a very common parasite and viable sheep production requires the extensive use of anthelmintic drugs. However, the emergence of drug-resistant parasites has stimulated the search for alternative control strategies to curb production losses. Lambs become infected soon after weaning and begin to control parasite burden within 8 – 10 weeks of continual infection. This control is an acquired characteristic mediated by the development of parasite-specific antibodies.

This paper describes the immunology associated with resistance and susceptibility, focussing on differential T cell activation that regulates the production of specific effector mechanisms. It continues by summarizing the methods used to identify genes that could be exploited as molecular markers of selection for resistance. In particular it focusses on the link between understanding the molecular immunology of infection and the identification of candidate genes for selection.

**Keywords:** sheep; parasite; gastrointestinal; immunity; resistance; genetics.

Parasitic gastroenteritis is perhaps the most pervasive problem facing the sheep agricultural industry. Demand for cheaper meat and diminishing pasture land has led to increasing stocking density (Taylor, 2012), and there is public and political pressure to minimize anthelmintic drug use ([www.vmd.defra.gov.uk/pdf/leaflet\\_anthelmintics.pdf](http://www.vmd.defra.gov.uk/pdf/leaflet_anthelmintics.pdf)). In addition, the anti-parasitic drugs used to control these common infections are increasing ineffectual because of the spread of drug-resistant parasites (Wilson and Sargison, 2007; Sargison et al., 2010). The economic impact of gastrointestinal parasites is related to increased drug and animal management costs, production losses in terms of decreased live weight (Wilson and Sargison, 2007), reduced fleece weight (Simpson et al., 2009), inefficient food conversion rates and reduced lamb survival (Armour et al., 1996).

The most economically important nematode parasite of sheep in cool temperate regions, including much of the UK and New Zealand, is *Teladorsagia circumcincta* (Brunsdon, 1988; Armour et al., 1996). This is the ‘brown stomach worm; adults are 7–12 mm long and feed on mucosal tissues and cellular secretions (Soulsby, 1982) of the abomasum. It is a ubiquitous, persistent parasite that is responsible for seasonal outbreaks of parasitic gastroenteritis, in particular among weaned lambs in spring (Gruner et al., 1994; Armour et al., 1996; Sargison et al., 2007). This species has a direct life cycle with no tissue migratory stage. The pre-infective larval stages (L1 and L2) feed on microorganisms in the soil and infection is acquired by ingestion of the L3 larvae by grazing sheep. Larvae enter the abomasal gastric glands 2–3 days after ingestion and develop into the pre-adult stages (L4 and L5) before they mature into sexually active adults 15–19 days later.

The primary pathology of *T. circumcincta* infection is associated with an inflammatory response to developing larval in the gastric glands that damages the tight junctions and stretches the mucosal lining, leading to mucosal hyperplasia (McKellar, 1993; Gruner et al., 1994). These changes cause reduction of digestive enzyme production and leakage of macromolecules and proteins across the damaged epithelium, resulting in hypoproteinemia (Lawton et al., 1996). The disease is characterized by anorexia, intermittent diarrhoea and dehydration, which may lead to emaciation and death (Stear et al., 2003; Kyriazakis and Houdijk, 2006).

The increasing problem of anthelmintic resistance in sheep nematodes has stimulated interest in non-pharmaceutical and sustainable methods of parasite control. Most approaches are aimed at reducing worm infection by limiting host-parasite contact, reducing worm establishment and persistence, and removing adult worms in the host. The animals most at risk from *T. circumcincta* infection are immunologically-naïve weaned lambs during their first grazing season (Stear et al., 1999). However, many sheep eventually control parasite colonization and egg production through the acquisition of protective immunity (Stear et al., 1999; Halliday et al., 2010), which takes up to 8 weeks of persistent exposure to infective larvae to establish (Seaton et al., 1989; Beraldi et al., 2008). The maintenance of protective immunity requires continual stimulation, and consequently the lack of infection over winter leads to waning of protection and subsequent reinfection in spring (Stear et al., 2000). However, yearlings control larval colonization and egg production more quickly than weaned lambs because of previous exposure to infection (Smith et al., 1985; Singleton et al., 2010).

### Effector mechanisms of protection

Protective immunity to *T. circumcincta* is largely mediated by parasite-specific antibodies (Smith et al., 1986; Huntley et al., 1998b; Stear et al., 1999), which act to expel adults worms and ensheathed larvae and exclude new larval colonization with minimal tissue-damaging inflammation (Macpherson et al., 2000). Several

studies identify IgA as the major class of antibody associated with control of *T. circumcincta* infection and egg production (Sinski et al., 1995; Strain et al., 2002; Halliday et al., 2007). The negative correlation of serum IgA antibody levels with parameters of infection e.g. faecal egg count (FEC) and adult worm numbers (Beraldi et al., 2008) is strong enough to suggest that it can be used as a selectable marker for resistance (Stear et al., 1999; Sayers and Sweeney, 2005; Shaw et al., 2012); indeed the CarLA saliva IgA antibody test is currently being marketed as ‘a powerful new tool for selecting sheep’ (<http://www.carlasalivatest.co.nz/>).

The association between IgA and infection relates to antibody levels within serum, but it is presumed that the biologically-active antibody is secretory IgA, which is actively secreted across the mucosal epithelium of the abomasum (Macpherson et al., 2008). The mechanisms of IgA action are not quite clear but there are indications that it can control larval colonization and development, and egg production (Stear et al., 2004; Lacroux et al., 2006; Halliday et al., 2007) by specific binding to both larvae and adults or to nematode secretions. There is even one report that suggests that secretory IgA can inhibit larval establishment by triggering eosinophil degranulation (Abu-Ghazaleh et al., 1989), despite the fact that the eosinophils and antibody are on different sides of the epithelial barrier. Other more likely mechanisms of protection have been identified including inactivation of metabolic enzymes (Gill et al., 1993) and feed-suppression that would result to reduced adult worm length and fecundity (Stear et al., 2004; Craig et al., 2007).

It is clear that IgE also plays a significant role in parasite expulsion as high levels of IgE anti-parasite antibody are negatively correlated with FEC (Huntley et al., 2001; Murphy et al., 2010). The action of IgE is thought to be through a classical Type 1 hypersensitive reaction mediated by mast cell proliferation (Stear et al., 1995; Miller, 1996; Greer et al., 2008) and degranulation of IgE-primed mast cells. Consequent release of vasoactive mediators and cytokines (Kawakami and Galli, 2002; Pochanke et al., 2007) leads to contraction of blood vessel and gut smooth muscle (Scott and McKellar, 1998), increased mucus production (Stear et al., 2003) and up-regulation of interlectins, that might block larval colonization and development (French et al., 2008). This is supported by such observations as significant increases in mast cell proteinase in the gastric lymph and the accumulation of globule leukocytes (degranulated mast cells) (Huntley et al., 1992) in infected, cured, reinfected ‘immune’ sheep (Stear et al., 1995; Huntley et al., 1998a).

Eosinophils have been shown to have a significant role in protection to gastrointestinal nematode infections of many species including *Strongyloides stercoralis* in mice (Galioto et al., 2006) and *Haemonchus contortus* in sheep (Balic et al., 2006; Robinson et al., 2010). However, their role in *T. circumcincta* is unclear as there is no relationship between numbers of adult *T. circumcincta* and tissue eosinophilia (Henderson and Stear, 2006), or FEC and circulating eosinophil numbers (Beraldi et al., 2008). The ambiguity is likely to be related to the fact that *T. circumcincta* causes little damage to the mucosal epithelium and therefore eosinophils cannot make contact with the parasites on the luminal side of the intestinal epithelium.

#### Regulation of effector mechanisms

Although antibodies and mast cells have the major effector role in the control of parasite infection, these effector mechanisms are regulated by the cytokine environment generated by antigen activated T cells (Patel et al., 2009). Indeed, antibody depletion of CD4<sup>+</sup> T cells abrogated nematode resistance of selected sheep lines (Peña et al., 2006); identifying the T cell involved in the immunological regulation of nematode development and egg production is critical in understanding the effector mechanisms of worm control. An extensive body of research using murine models has highlighted the role of Th2 T cells in the control of

gastrointestinal nematode infections (Grencis, 1997; Gause et al., 2003; Anthony et al., 2007; Maizels et al., 2009). Balb/c mice generate a highly polarized Th2 response that controls *Heligmosomoides polygyrus* and *Trichuris muris*; whereas the same parasites persistently infect C57BL/6 and AKR mice that produce a greater Th1 inflammatory response (Maizels and Yazdanbakhsh, 2003; Reynolds et al., 2012). Studies in sheep and cattle using acute challenge of infected/cured/reinfected ('immune') animals with *T. circumcincta* (Craig et al., 2007), *H. contortus* (Miller and Horohov, 2006; Lacroux et al., 2006; Ingham et al., 2008), *Trichostrongylus colubriformis* (Pernthaner et al., 2005; Hein et al., 2010) and *Ostertagia ostertagi* (Gasbarre et al., 2001; Claerebout et al., 2005) confirmed the murine data and associated a Th2 polarized immune response with parasite control. Th2 immunity has also been implicated in the acute immune response to primary infection with *H. contortus* in the intrinsically-resistant BBB breed of sheep but not in the intrinsically-susceptible INRA breed (Terefe et al., 2007). Similarly, an acute Th2-cytokine profile is associated with control of infection in sheep lines selected for resistance to *T. colubriformis* (Pernthaner et al., 2005).

### Th1 and Th2 responses

The archetypal Th2 cytokine (Mosmann et al., 1997) is interleukin (IL)-4 and is probably the single most important cytokine in the immunological control of gastrointestinal parasite infection (Finkelman et al., 2004; Reynolds et al., 2012). Firstly, it is critical to the signalling pathway that promotes maturation of naïve CD4<sup>+</sup> T cells into the Th2 phenotype (Fig. 1) through the phosphorylation of signal transducer and activator of transcription (STAT)6 and the up-regulation and activation of the major Th2 transcription factor GATA3 (Zheng and Flavell, 1997; Zhu et al., 2010). Second, it functions to drive B cells into high rate antibody synthesis, promotes immunoglobulin heavy chain switch from IgM to IgE and IgA (Fig. 1) as well as stimulating mast cell maturation and proliferation (Finkelman et al., 1990; Nelms et al., 1999; Ansel et al., 2006). Indeed immunity to *H. polygyrus* is diminished by anti-IL-4 antibody administration and abolished by blockade of the IL-4 receptor (Urban et al., 1991).

IL-13 and IL-5 are also important in controlling gastrointestinal nematode parasites (Fig. 1). IL-13 acts in concert with IL-4 by stimulating IgE class switching, promoting tissue healing fibrosis and enhancing worm expulsion by increased mucosal permeability, mucus production and muscle contraction (Madden et al., 2002; Wynn, 2003; Meeusen et al., 2005). IL-5 stimulates the maturation of eosinophils. Up-regulation of these two cytokines after *T. colubriformis* infection (Meeusen et al., 2005; Lacroux et al., 2006) coincided with increased IgE and IgA production (Kooyman et al., 2000) and eosinophilia (Henderson and Stear, 2006).

The archetypal Th1 cytokine (Mosmann et al., 1997) is interferon (IFN)  $\gamma$  and in many host-parasite systems an increase in this cytokine is associated with persistence of parasite infection and disease (Maizels and Yazdanbakhsh, 2003; Anthony et al., 2007; Dawson et al., 2009). In cattle, IFN $\gamma$  inhibited host protective antibody responses to *Strongyloides papillosus* larvae, resulting in an improvement of worm survival and increased egg production (Nakamura et al., 2002). This link between IFN $\gamma$  and susceptibility is thought to be through its role in inhibiting Th2 differentiation and down-regulating IL-4 (Bancroft and Grencis, 1998; Pulendran, 2004). The other major Th1 cytokine associated with nematode infection is IL-12 (Pearlman et al., 1995; Bancroft et al., 1997; Rotman et al., 1997). It controls the maturation of naïve CD4<sup>+</sup> T cells to Th1 cells; IL-12 binding to its receptor, IL12R $\beta$ 1/R $\beta$ 2 (Fig. 1) activates STAT4 (Fig. 2) and triggers the production of the Th1 transcription factors T-bet (TBX21) and HLX; these in turn promote the production of IFN $\gamma$ .

The view that a Th1 response is associated with susceptibility and a Th2 response with resistance and that the balance of susceptibility and resistance is simply a matter of Th1/Th2 dichotomy has been challenged in recent years. Some ruminant studies have shown constant or increased expression of IFN $\gamma$  and IL-12 despite a predominant Th2 response (Meeusen et al., 2005; Pernthaner et al., 2005) in *H. contortus* infection, and IFN $\gamma$  expression was unaffected by *T. circumcincta* infection of either immune (infected/cured) or 'naïve' lambs (Craig et al., 2007). This view is strongly supported by the identification in humans and mice of an expanding range of CD4<sup>+</sup> T cell subsets (Zhu et al., 2010), including regulatory T cells (Tregs) and Th17 cells, and their tendency towards plasticity (Nakayamada et al., 2012; Panzer et al., 2012).

### Treg and Th17 responses

The effector mechanisms that develop in the presence of Th2 – associated cytokines are clearly responsible for the control of gastrointestinal nematodes; it is equally clear that uncontrolled Th2 activation can result in autoimmune pathology (Maizels and Yazdanbakhsh, 2003; D'Elia et al., 2009). One of the ways in which the immune response is controlled, to prevent the pathological consequences of prolonged immune activation, is by the development of induced Tregs (Sakaguchi, 2004; Belkaid and Rouse, 2005; Belkaid and Tarbell, 2009). Tregs can protect against this consequence (Tang and Bluestone, 2008) by their ability to suppress the immune response (Sakaguchi, 2000; Belkaid and Rouse, 2005) with IL-10 and TGF $\beta$ , cytokines that are responsible for much of the plasticity of the T cell response (Letterio and Roberts, 1998; Gorelik and Flavell, 2002; Ouyang et al., 2011).

Tregs have been shown to be critical for the clinical outcome of helminth infection (Belkaid and Tarbell, 2009). Resistance to helminths in mice seems to be determined by a balanced Th1/Th2/Treg response; unbalanced modified Th2 (high Th2/Treg) and uncontrolled Th1 (high Th1) resulted in persistent infection and clinical disease (Maizels and Yazdanbakhsh, 2003; Belkaid and Tarbell, 2009). CD4<sup>+</sup> Treg cells are usually identified as expressing IL2RA (CD25, IL-2 receptor  $\alpha$  chain) and the transcription factor FOXP3 (Hori et al., 2003; Fontenot et al., 2005). The balance in expression of the two transcription factors FOXP3 and GATA3 seems to control CD4<sup>+</sup> T cell differentiation (Ziegler, 2006; Wang et al., 2011) including during chronic nematode infection (Zheng and Rudensky, 2007). In *H. polygyrus* infection of mice, an early Th2-dominated cytokine profile shifted to a Treg response by day 28. This was marked by expansion of FOXP3<sup>+</sup> cells, elevated IL-10 and higher numbers of TGF $\beta$ <sup>+</sup> T cells (Finney et al., 2007). Treg activity was also demonstrated in human infections with the filarial nematodes *Onchocerca volvulus* (Korten et al., 2008) and *Litosomoides sigmondontis* (Taylor et al., 2005); and in sheep infected with *T. circumcincta* (Craig et al., 2007), *H. contortus* and *T. colubriformis* (Ingham et al., 2008).

Th17 cells have recently emerged as a distinct T cell subset that produces the inflammatory cytokines IL-17A and IL-21 but not IFN $\gamma$  or IL-4. This subset is particularly important in the induction of inflammation that controls bacterial infections, especially at mucosal sites (Korn et al., 2009). However, inappropriate activation of Th17 cells leads to autoimmune inflammatory diseases like inflammatory bowel disease (IBD), asthma and rheumatoid arthritis (Weaver et al., 2007; Peck and Mellins, 2009). The cytokine IL-6 is critical for Th17 development (Kimura and Kishimoto, 2010) as it drives the TGF $\beta$ -induced naïve T cells to differentiate to Th17 instead of other T cell subsets (Mangan et al., 2006; Veldhoen et al., 2006). IL-6 also up-regulates IL-23R

and works synergistically with IL-23 (IL23A/IL12B); another cytokine that promotes Th17 inflammation (Fig. 2) (Kastelein et al., 2007; Ahern et al., 2010).

In a recently reported series of experiments concerned with the immunopathology of chronic *T. circumcincta* infection, Blackface lambs from parents with genetic variation for FEC were trickle-infected with L3 larvae over 12 weeks. Lambs were identified with a range of susceptibilities as assessed by adult worm count at post mortem, FEC and IgA antibody levels. Histopathology showed only minor pathology in the abomasal mucosa in resistant animals (low/no adult worms and FEC, high IgA) with a low level lymphocyte infiltration; but in susceptible lambs (high adult worms and FEC, low IgA), major pathological changes were associated with extensive inflammatory infiltration. RT-qPCR assays on the abomasal lymph node revealed significantly high levels of IL-6, IL-21 and IL-23A in susceptible sheep and a positive correlation with adult worm count and FEC; consistent with the hypothesis that the inability to control L3 larval colonization, adult worm infection and egg production is due to the activation of the inflammatory Th17 T cell subset (Gossner et al., 2012a; Gossner et al., 2012b).

### Breeding for resistance to gastrointestinal nematodes

Resistance is defined as the ability of a host to initiate and maintain responses to suppress the establishment of parasites and /or eliminate the parasite load (Woolaston and Baker, 1996). Breeding for resistance utilizes sheep genetic variation to select for resistant to nematode parasites, and has been the subject of many reviews covering related work (Albers and Gray, 1987; Woolaston and Baker, 1996; Stear et al., 1997; Stear et al., 2006; Davies et al., 2006). Selection for resistance has traditionally been based on quantitative measurements of phenotypic traits. The practical use of indicator traits is best exemplified by the FAMACHA scoring system (van Wyk and Bath, 2002) to assess the degree of anaemia as a clinical manifestation of *H. contortus* infection. The method involves comparing the colour of the eye conjunctiva against an eye colour chart (Gauly et al., 2004; Kaplan et al., 2004), then marking a score that corresponds to the need to administer anthelmintic drugs to the affected animal. Evaluation of estimated breeding values for FAMACHA scores indicate its heritability (Riley and Van Wyk, 2009) and has now been used as a phenotypic marker for selection in Brazil (Molento et al., 2009). However, FEC has been the most widely-used parameter in identifying sheep nematode resistance (Smith et al., 1984; Gill, 1991; Gruner et al., 2004; Davies et al., 2005). Heritability values vary from 0.30 - 0.48 in *T. circumcincta* (Stear et al., 2009), *T. colubriformis* (Sreter et al., 1994; Douch et al., 1996) and *H. contortus* (Gruner et al., 2004) making it a viable indicator trait for selection. The genetic component of FEC is further evidenced by its association with three different genotypes at the diallelic adenosine deaminase locus (Gulland et al., 1993) and major histocompatibility complex (MHC)-linked microsatellites in a wild population of Soay sheep (Beraldi et al., 2007). Moreover, FEC is repeatable over time and heritable by six months (Bishop et al., 1996; Davies et al., 2005). There are other potential phenotypic traits that could be used for selection for *T. circumcincta* resistance, including adult worm count and worm length with reported heritability of 0.14 and 0.62 respectively (Stear and Bishop, 1999). Plasma IgA has been found to have high heritability and repeatability (Strain et al., 2002) and eosinophil levels might be useful, with estimated heritability in 4-5 month old lambs of 0.43-0.48 (Henderson and Stear, 2006).

The identification of molecular markers is potentially a more reliable approach with such markers being defined by association to a quantitative trait such as FEC (Douch et al., 1996). There are three general



approaches in identifying causal mutation effect for quantitative traits: quantitative trait locus (QTL) mapping, genome-wide association studies (GWAS) and candidate gene analysis (Pemberton et al., 2011). QTL identification involves mapping a gene for a trait on genome region with the use of known DNA markers such as microsatellites or single nucleotide polymorphisms (SNPs) (Beh et al., 2002). The traditional strategy of QTL mapping was to use linkage analysis to map a QTL with microsatellite markers. However, microsatellites are not as abundant as SNPs in the genome hence low marker density genome scans generally yield crude estimates of QTL location and magnitude (Slate et al., 2009). QTLs related to gastrointestinal worm resistance have been identified at the genome- or chromosome-wide level. Regions of the ovine genome on sheep chromosome 3 (OAR3) were consistently associated with resistance to sheep strongyles (Davies et al., 2006; Beraldi et al., 2007; Marshall et al., 2009; Dominik et al., 2010) and loci on OAR4 (Matika et al., 2011) and OAR6 (Beh et al., 2002; Beraldi et al., 2007) were also linked to parasite resistance. It is clear from the biology and immunology that resistance to *H. contortus* and *T. circumcincta* is an acquired characteristic (Beraldi et al., 2008; Singleton et al., 2010) related to the development of an adaptive immune response controlled by differential T cell activation (Gossner et al., 2012a). Furthermore, different types of immune response give rise to different disease outcomes. Consequently, interesting QTLs are also those on OAR1 and OAR11 (Marshall et al., 2009; Coppieters et al., 2009), which include genes such as RORC (ROR $\gamma$ ) and STAT3, transcription factors controlling Th17 maturation and function; and TBX21 and STAT5, transcription factors associated with Th1 and Th2 respectively. In addition, a significant QTL is on OAR20; this contains ovine MHC genes, and many studies have found associations between MHC and parasite resistance. Genome-wide association studies for gastrointestinal parasite resistance in sheep have used the current state-of-art SNP chip that contains ~50,000 SNPs (Kijas et al., 2009); one of the few studies has revealed novel QTLs associated with resistance to *H. contortus* and *T. colubriformis* located within OAR6, OAR14 and OAR22 in African Red Maasai sheep (Silva et al., 2012).

Candidate gene analysis evaluates a relationship between a trait and a mutation in specific functional genes selected for the differential expression in relation to a phenotypic trait. These candidate genes are selected, based on their established or supposed function using causal association tests or by differential expression assessed by transcriptomics such as RNAseq and/or microarray analysis (Pemberton et al., 2011). A number of genes have been linked with the ability of sheep to resist infection to GI parasites primarily based on FEC as the phenotypic trait. The three most studied molecular markers linked to FEC are genes of the MHC complex (Schwaiger et al., 1995; Buitkamp et al., 1996; Sayers et al., 2005a; Keane et al., 2007; Lee et al., 2012), IFNG (IFN $\gamma$ ) (Coltman et al., 2001; Sayers et al., 2005b) and IL-4 (Benavides, V et al., 2009). The association of MHC with differential response to infection is attributed to MHC polymorphism and involvement of MHC gene products with the induction and regulation of the immune response (Cresswell, 1994). Several *Ovar-D* (MHC class II) alleles have shown significant associations with low FEC under both natural and experimental infection protocols, including the allele *Ovar-DRB 257* (Paterson et al., 1998) and *Ovar-DY* (Buitkamp et al., 1996). Susceptibility was also associated with the MHC Class II locus where high FEC was observed in New Zealand sheep carrying *Ovar DQA2\*1201* allele (Hickford et al., 2011). However, one of the best-studied genetic markers is *Ovar DRB1\*1101* (also known as G2 and *Ovar-DRB1\*0203*) (Schwaiger et al., 1995; Sayers et al., 2005a; Hassan et al., 2011); substitution of the most common alleles by *DRB1\*1101*

resulted in a 22 - 81 fold reduction in *T. circumcincta* FEC. Carrier lambs with *DRB1\*1101* had lower adult worm burden and higher mast cell and plasma lymphocyte count.

The studies on the physiology of the immune responses associated with resistance and susceptibility are also likely to identify potential candidate markers for selection. Th2 T cell differentiation and consequent high antibody production is associated with control of parasite colonization, egg production and therefore 'resistance'. Genes associated with differential T cell activation involve a range of cytokines (Fig. 2) and their complex receptors. These trigger the phosphorylation of subset-specific STATs that control the expression of T cell subset-specific transcription factors. Interestingly, the pathological and immunological characteristics associated with chronic *T. circumcincta* infection and susceptibility have some similarities to that found with inflammatory diseases in other species, including the human inflammatory diseases of the gut (Xavier and Podolsky, 2007; Cho, 2008; Khor et al., 2011) and the lung. Indeed, *Trichuris muris* in susceptible AKR mice induced transcriptional changes strikingly similar to models of IBD and human IBD including predominantly Th1/Th17 T cell activation pathways (Levison et al., 2010). Consequently, variation of many of the genes associated with differential T cell activation (Van Limbergen et al., 2007) are linked to one or more of the chronic inflammatory diseases, including IL23/IL23R and Crohn's Disease (Kobayashi et al., 2008; Lees et al., 2011), STAT3, STAT4 and GATA3 with ulcerative colitis (Ohtani et al., 2010), IL12B and IL12RB1 with IBD (Ford et al., 2012), and TBX21 and HLX with asthma (Suttner et al., 2009).

## Conclusions

Breeding for resistance, or away from susceptibility, is an attractive alternative to increased anthelmintic drug use for the control of gastrointestinal nematode parasites. Chronic exposure to infectious larvae eventually leads to the reduction of larval colonization and egg production in the majority of animals, indicating that the adaptive immune response plays a major role in parasite control. The details of that adaptive immune response are crucial because different types of immune response results in different clinical outcomes. IgE and IgA anti-nematode antibodies play a significant role in protection, and antibody levels are optimized in those sheep that generate a type 2 T cell response. In contrast, chronically-infected sheep produce an inflammatory Th1 or Th17 response that inhibits antibody production, leading to persistent parasite infection. Consequently, the physiological pathways associated with the induction of the adaptive immune response and differential maturation of T cells are likely to contain candidate genes as potential selectable markers for resistance to *T. circumcincta*.

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Figure 1

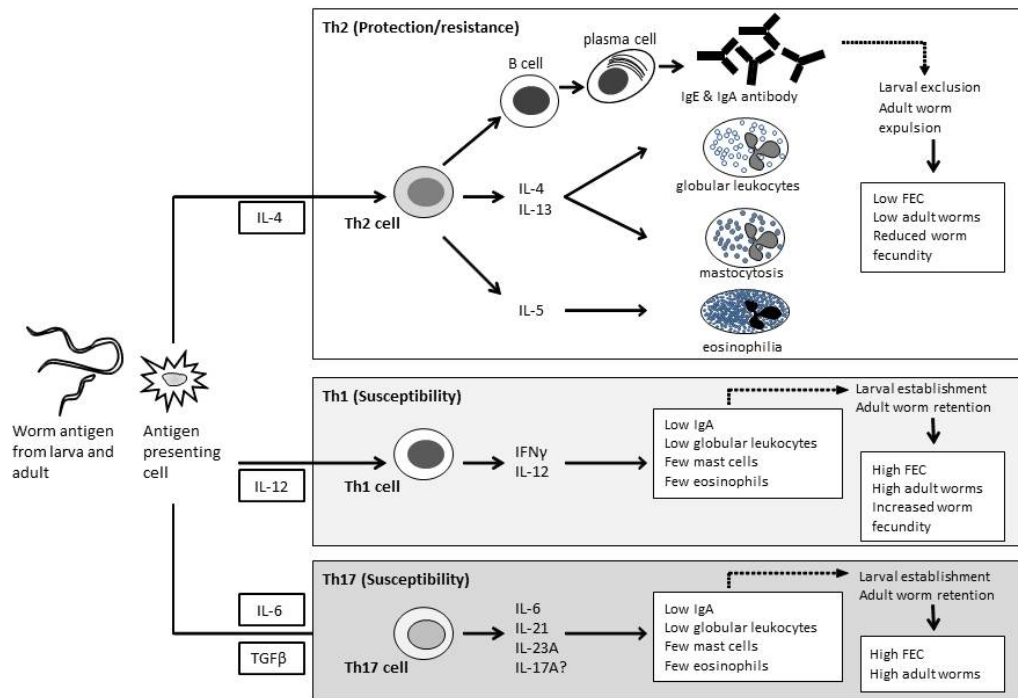


Figure 2

